A COMPARATIVE STUDY OF METFORMIN VERSUS INSULIN IN MANAGEMENT OF GESTATIONAL DIABETES MELLITUS

Submitted by

FATHIMA HABEEBA T.E

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1. INTRODUCTION

Gestational Diabetes Mellitus (GDM) is a condition in which women without previously diagnosed diabetes exhibit elevated blood sugar level during pregnancy. GDMcan be defined as glucose intolerance that begins or isthe first recognized during pregnancy. The American Diabetes Association (ADA) defines GDM as “the glucose intolerance of any degree with onset or recognition during pregnancy”(Magon N and Seshiah V 2011). Uncontrolled blood sugar complicates about 1-4% of all pregnancies, which may range from mild degree of hyper glycaemia to insulin dependent diabetes. GDM may be caused by reduced pancreatic β-cell function, which results from the full spectrum of causes of β-cell dysfunction in young women or it may be considered as an insulin resistant state, possibly due to the placental production of progesterone, cortisol, prolactin and other hormones which interfere with normal glucose metabolism (Setji TL et al. 2005). Obesity, previous history of GDM, family history of diabetes mellitus, racial origin, increased maternal age, previous macrosomic baby, polycystic ovary syndrome and twin pregnancy are considered as main risk factors for developing gestational diabetes (Cheung KW and Wong SF 2012).GDM is one of the most occurring metabolic diseases of pregnancy and the prevalence of GDM is variable depending on the population was being studied and which screening strategies or diagnostic criteria were followed.A study conducted in 2013 by the International Diabetes Federation estimated that worldwide 16% of live births were complicated by hyperglycemia during pregnancy (Kampmann, U et al, 2015).The prevalence of GDM is increasing worldwide with the dramatic increase in the prevalence of overweight and obesity in women of childbearing age. The prevalence of GDM in Indian population varies from 3.8 to 21% in different parts of the country and prevalence in South India has increased dramatically recently to 16 % (Zhu, Y. and Zhang, C., 2016). The high prevalence of GDM in South India may be due to obesity, family history of diabetes mellitus, sedentary lifestyle, genetic predisposition and dietary habits.

Untreated hyperglycemia in pregnancy may lead to serious maternal complications such as pregnancy induced hypertension, pre-eclampsia and increased risk of caesarean delivery. Neonatal complication includes macrosomia, neonatal hypoglycemia, perinatal mortality, congenital malformations, hyperbilirubinemia, polycythemia, hypocalcemia and respiratory distress syndrome (Setji TL et al. 2005).These complications may be reduced either by appropriate diet, mild physical exercise or through proper medication management.Insulin has pivotal role in the management of GDM since many years, due to its efficacy to control elevated blood sugar level (Metzger 2007). Insulin can be administered according to the pattern of glucose concentration in order to control the elevated blood sugar level. An initial dose of subcutaneous administration of NPH insulin (4 units) could be used, if the fasting blood glucose concentration is greater than 90 mg/dl, or when the 1-hour postprandial blood glucose concentration is greater than 120 mg/dl and the dose can be titrated on the follow up visits according to the glycemic status.However, the difficulty in medication administration with multiple daily injections, potential for hypoglycemia, increase in appetite and weight gain make this therapeutic option cumbersome for many pregnant women with GDM (Magon, N. andSeshiah, V., 2011).

2. REVIEW OF LITERATURE

Alfadhli et al 2015, conducted prospective descriptive study of pregnant Saudi women presenting at the Maternityand Children Hospital, Medina, Saudi Arabia to determine the prevalence of GDM in Saudi women and to assess risk factors and pregnancy outcomes. Early screenings showed abnormal glucose in 211 of 954 women (22.1%). In 445 women, the OGTTshowed GDM in 183 women (39.4%). GDM cases identified by OGTT and by early screening increased the rate of GDM to 51% (292 women). Older maternal age, higher body mass index, higher blood pressure, past GDM, history of delivering a malformed child, and family history of diabetes were found the main risk factors for GDM.

Munshi et al 2014, conducted prospective comparative study to assess the efficacy of metformin in the management of GDM and to compare maternal fetal outcome between metformin and in insulin in GDM. The study showed no significant difference in GDM with the use of metformin or insulin. 84% of insulin group had good glycemic control whereas in metformin group, 72%, achieved euglycemic state. Maternal and fetal outcome were also comparable between the two treatment groups. The study concluded that GDM, glycemic control can be done a combination of MNT (Medical Nutrition Therapy), exercise and using the oral drug metformin without risk of teratogenicity or maternal hypoglycemia and with comparable neonatal outcome.

Kalra et al 2013 conducted study to evaluate the prevalence of GDM using diabetes in pregnancy in Western Rajasthan and it was found to be 6.6%. Maternal and fetal complications in GDM group were found much higher than in the non-GDM group. Hypertension, vaginal candidiasis and abruption placentae were commonly observed maternal complications while macrosomia and still birth were found to be occurred in fetus.

Waheed et al 2013, conducted randomized clinical trial to compare the efficacy of metformin with insulin in the management of pregnancy with diabetes at a medical institutein Pakistan.Fasting blood sugarlevel after 1 month was controlled in 64.7% patients in Insulin group and in 79.4% in metformin group. Fasting blood sugar level at term, remained controlled in 88.2% patients in Insulin group and 79.4% in metformin group. Comparison of post-treatment HBA1C level depicts that diabetes controlled in 79.4% patients in Insulin group while in 82.3% patients of metformin group. The study found that there was no marked difference in efficacy of metformin and insulin in controlling diabetes in pregnantpatients in two groups.

Niromanesh et al 2012, conducted a randomized clinical trial to evaluate the effect of metformin and insulin in glycemic control and compare pregnancy

outcome in women with gestational diabetes mellitus. The two treatment groups were found to have similar in mean FBS and postprandial measurements throughout study period. Also the neonates of metformin group had less rate of birth weight than insulin group. Maternal weight gain was observed to be reduced in the metformin group. Metformin was found an effective and safe alternative treatment to insulin for womenwith GDM and the study did not show significant risk of maternal or neonatal adverse outcome with the use of metformin.

Bener et al 2011, conducted prospective cohort study at antenatal clinics of the Women's Hospital in Qatar to determine the prevalence of GDM and to compare maternal &neonatal complications among women with GDM and non-GDM pregnant women. 2056 pregnant women who attended the antenatal clinics of the Women's Hospital were surveyed during the study period and the prevalence of GDM in Qatar was 16.3%. The study findings revealed that GDM was found to be higher in women in Qatar and theywere at increased risk of developing maternal and neonatal complications. The advanced maternal age, low monthly income, family history of diabetes, and obesity were found the main significant risk factors for GDM.

Seshiah 2008 et al conducted a prospective study to found the prevalence of GDM in the urban, semi urban and ruralareas in South India. The prevalence of GDM was found to be 17.8% in the urban, 13.8% in Semi urban and 9.9% in rural areas. They concluded that high prevalence of GDM in urban area may be due to the increased maternal age, obesity and sedentary life style. Also less prevalence in rural area may be due to the less mechanized and agriculture based life style. This study pointed that increased BMI is a main risk factor for the development of GDM.

Rowan et al 2008, Australian study conducted randomized trial to assess the efficacy and safety of Metformin and Insulin of GDM. 751 women (371 received metformin and 378 received insulin) who were randomized between 20 and 33 weeks of pregnancy. The metformin failure rate was 7.4%, in which a

second diabetic agent was needed to maintain controlled glucose levels. Although there was no difference in mean fasting blood glucose levels between groups, those on metformin had lower 2-hour postprandial glucose levels. There was no difference in the rate of preeclampsia. Infants of women randomized to metformin found to be experienced a lower rate of hypoglycemia when compared with that of insulin.

Crowther et al 2005, conducted the study under the Australian Carbohydrate Intolerance Study in Pregnant Women Trial Group (ACHOIS) to find out the effect of treatment GDM on pregnancy outcomes. The sample size consisted of 490 women intervention group and 510 were control group. The study was done with 75-g OGTT according to WHO criteria. The rate of serious perinatal outcomes among infants decreased significantly from 4% to 1% after intervention. In ACHIOS trial the rate of cesarean section were similar between intervention and control group. There was an increased incidence of induction of labor in the intervention group and they concluded that treatment of GDM reduces serious perinatal morbidity and may also improve the woman's health-related quality of life.

3. AIM AND OBJECTIVES

The aim of the study was to assess and compare the glycemic control, maternal outcome and neonatal outcome in gestational diabetic women treated with metformin and insulin, with the following objectives.

- To assess the prevalence of gestational diabetes mellitus among pregnant women attending obstetrics and gynecology department of a teaching hospital for antenatal care.
- To assess the demographic details of the gestational diabetic women who were enrolled for the study after confirmation of the diagnosis.
- To assess and compare the glycemic control in gestational diabetic women treated with metformin andinsulinat 24-28 weeks and 36-38 weeks of pregnancy.

- To assess and compare the maternal outcomes of gestational diabetic women treated with metformin and insulin.
- To assess and compare the neonatal outcomes in neonates delivered by gestational diabetic mother treated with metformin and insulin.

4. SCOPE OF THE STUDY

Subcutaneous insulin administration is the standard treatment for achieving adequate glucose level in GDM, which is not controlled by diet modification.The use of oral hypoglycemic agents like metformin in pregnancy has opened new vistas for management of diabetes during pregnancy.Metformin has already got a gynecological off-label use in the treatment of Poly Cystic Ovary Syndrome (PCOD). Documented evidences of safety and efficacy of metformin from the preclinical as well as human studies brought metformin as a new option in the pharmacotherapy of gestational diabetes mellitus.Metformin is a cost-effective oral hypoglycemic agent, which may be a more logical alternative to insulin for women with GDM who are unable to cooperate with the adverse effects of insulin. Metformin reduces the blood glucose level by inhibiting gluconeogenesis and also reduces insulin resistance, particularly in liver and musco-skeletal tissue.Several studies demonstrated in different population revealed that metformin is beneficial in GDM for maintaining blood sugar level in normal range; also as safe as insulin in the pharmacological management of GDM. Also studies point that, the children of gestational diabetic women treated with metformin are found to be healthier in the neonatal period than that of Insulin treated.Metforminhas been well utilized in pharmacotherapy of gestational diabetes in western countries, whereas in Indian scenario fewer doctors have started prescribing metformin in the management of GDM.

5. METHODOLOGY

It was a prospective observational study conducted in the obstetrics and gynecology department, teaching hospital, after getting approval from

Institutional Ethics Committee. The diagnosis of the gestational diabetes mellitus at the time of enrolment was confirmed by two step approach according to American Diabetes Association (ADA) guideline. Allpregnant women visited the OBG department during the study period, who satisfied with the inclusion criteria underwent 50gm Glucose Challenge Test (GCT). If the value was greater than 139mg/dl, then they were send for 75gm Oral Glucose Tolerance Test (OGTT).The values of GCT were consideredasnormal: 95mg/dl at 0 minutes, 180mg/dl at one hour, 155mg/dl at second hour, 140mg/dl at third hour. If the participant presented 2 or more altered results on OGTT, the diagnosis of GDM was confirmed. Women with GDM were given with counselling on diet and advised for moderate physical exercise. Repeated the Fasting Blood Sugar (FBS) and Post Prandial Blood Sugar (PPBS) after two weeks. Those with FBS greater than 120mg/dl and PPBS greater than 140 mg/dl, were recruited in the study and were referred to a physician to cross check the diagnosis and to start with appropriate drug treatment.

The selection of participant for the study was based on the following criteria:-

5.1. Inclusion Criteria

- The patients who were diagnosed with gestational diabetes mellitus according to the diagnostic criteria recommended by the American Diabetic Association (ADA) guidelines.
- 18-40 years old with singleton pregnancy and gestational age between 20-34 weeks,who did not maintain fasting blood glucose level less than 95mg/dl or 2-hour post prandial blood glucose less than 120mg/dl by medical nutritional therapy during one week

5.2. Exclusion Criteria

- Participants with history of underlying diseases like renal, cardiovascular, liver, and autoimmune diseases or other terminal diseases.
- Participants with contraindication to metformin, foetal anomaly, essential hypertension, gestational hypertension, pre-eclampsia, foetal growth restrictions and ruptured membranes, Intra uterine growth retardation,

previous history of diabetes, twin pregnancy, treatment initiated before 12 weeks or after 34 weeks of gestation.

5.3. Institutional Ethics Committee Approval

The Institutional Ethics Committee of the research center had approved the study protocol and permitted to conduct the study atdepartment of obstetrics and gynecology through letter No: IEC/MES/51/2014dated 29-09-2014.

The study was well explained to participants andwritten informed consent in vernacular language was obtained from each participants before enrolment. Demographic and clinical data were collected by patient direct interview and investigational reports were collected from medical records department. The Demographic data includes age, body weight, height, body mass index, history of diabetes mellitus, history GDM, number of pregnancies were collected from medical records and by patient direct interview. The values of GCT and OGTT were recorded. FBS, PPBS and Hb1Ac were recorded at the baseline and end of the study.

The maternal characteristics such as parity, total weight gain during pregnancy, mode of delivery, gestational week at delivery and pre term delivery also were recorded. Neonatal characteristics such as birth weight, head circumference, mid-upper-arm circumference, admission to neonatal intensive care unit (NICU), perinatal death, umbilical artery pH, 5 min Apgar score, hyperbilirubinemia, hypocalcemia, hypoglycemia, respiratory distress syndrome, birth defect and congenital anomalies were recorded for both drug treated groups.The collected data from each patient were recorded in data collection form and were spread into an excel sheet. The mean ± SD values of the each variable was calculated. The data were analyzed using appropriate software to find out the statistical significance. Parameters with $P<0.05$ were considered as significant and those with $P<0.01$ were considered as highly significant.

6. RESULTS AND DISCUSSION

The result obtained from the study show that all participants in both drug treatment group achieved the goal of drug therapy. The effect of two drug treatment on FBS are given in Table - 1. Among 3972 pregnant ladies visited in

the obstetrics and gynecology department during the study period, 286 were diagnosed to have GDM. Out of 286 GDM patients, 140 were treated with insulin and 146 were treated with metformin.Out of 140 patients in the insulin group, 54 were with ideal body weight,50 were overweight and 36 were found to be obese. In the metformin group 36 were with ideal body weight, 91 were overweight and 19 were obese.In the insulin treatment group 31 had family historyof diabetes mellitus; whereas 19 participants in the metformin group had family history of diabetes mellitus.In the insulin treatment group 60 had family history of GDM; whereas in the metformin group 17 had family history of GDM.In thepresent study, mean GCT value in insulin group was 166.54 mg/dl and mean GCT value in metformin group is 157.94 24 mg/dl.

Table – 1 Comparison of FBS values of gestational diabetic women in different treatment group

Groups	N	FBS			Mann Whitney U Value	P Value
		Mean	SD	Median (IQR)		
24-28 weeks						
Insulin	140	122.31	26.14	113 (105-124)	6257	<0.001
Metformin	146	108.99	8.11	105 (104-112)		
36-38 weeks						
Insulin	140	94.68	16.06	90 (87-98)	9530	0.320
Metformin	146	90.20	6.37	90 (88-95)		

In the present study, of 140 patients in the insulin group 25 (17.9%) were had gestational age less than 37 weeks, whereas in the metformin group 10 had a gestational age of more than 37 weeks.The mean of weight gain during pregnancy in Insulin group was 10.04 ± 2.31 Kg and that of metformin group was 8.95 ± 1.65 Kg. Among 140 neonates in the insulin group 5(3.6%)babies had macrosomia, whereas in the metformin group none of them had

macrosomia.Out of 140 patients in the insulin group 29had normal delivery, 34had assisted delivery and 36 had done LSCS. Whereas in the metformin group 70 were normaldelivery, 61were assisted and 159 were LSCS. The mean of head circumference in insulin group was 33.08 cm and that of metformin group was 33.32 cm. The mean abdominal circumference ininsulin group was 32.00 cm and that ofmetformin group was 32.35 cm. The mean mid upper arm circumference ininsulin group was 11.79 cm and that ofmetformin group was 11.10cm. The mean chest circumference in theinsulin group was 32.08 cm and that ofmetformin group was32.57 cm.

In insulin group the mean of neonatal arterial blood glucose level at first hour was 53.19 mg/dl and that ofmetformin group was 48.47 mg/dl. In insulin group the mean of neonatal blood glucose level at second hour was 57.79 mg/dl and that of metformin group was 56.59 mg/dl.Out of 140 neonates in the insulin group 28(20.0%)had neonatal hypoglycemia, whereas in the metformin group none of the new born had neonatalhypoglycemia. The mean serum bilirubin in neonatesof insulin group was 16.22 and that of metformin group is 12.80. The mean serum calciumof neonates ininsulin group was 2.22 and that of metformin group was 2.24. Among 140 neonates in the insulin group, 32neonates had 5 minute Apgar score less than 7 and108had 5 minute Apgar score more than 7;whereas in the metformin group none of them had5 minute Apgar score less than 7. Out of 140 neonates in the insulin Group, 25 (17.9%)had developedpolycythemia; whereas in the metformin group none of them had polycythemia.

Out of 140 neonates in the insulin group 25 (17.9%)neededNICU admission; whereas in the metformin group 5 (3.4%) needed NICU admission. Among 140 neonates in the insulin group, 16 (11.4%)hadlung complication; whereas in the metformin group none of them hadlung complication. Among 140 neonates in the insulin group 12 (8.6%)had birth injuries; whereas in the metformin group, 65 (44.5%) had birth injuries.

7. CONCLUSION

The overall result from the study says that metformin was found as effective as insulin in controllingglycemic status in GDM women. metformin was found to be effective in reducing maternal and neonatal complications when compare to that of insulin treated group. Also the affordable cost and convenience of oral administration make metformin more patient friendly and thus to increase adherence with drug therapy can bring better patient compliance. There formetformin can be prescribed for pregnant women with gestational diabetes mellitus in order to bring down the elevated blood glucose level to normal range so that the further complications of GDM may be minimized.

8. REFERENCES

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ANNEXURE

MES MEDICAL COLLEGE, PERINTHALMANNA

INSTITUTIONAL ETHICS COMMITTEE

No.IEC/MES/ 51/2014 Date. 29 Sep 2014

To Mrs. Fathima Habeeba T.E
Rahmath House
Thariode North (PO)
Wayanad (DT), Kerala

Dear Habeeba

Sub:. Research proposal – approval of the Institutional Ethics Committee – regarding

I am happy to inform you that your research proposal on **"A comparative study of metformin Vs insulin in management of gestational diabetes mellitus. "** was carefully reviewed by the Institutional Ethics Committee met on 29 Sep 2014. The decision of the committee is shown below:

Decision: The proposal is approved.

In this connection, the Committee would like to request you to strictly follow the Ethical Guidelines for Biomedical Research on Human Participants,2008 by ICMR/GOI

Wish you good luck

Yours sincerely

CHAIRMAN
Institution Ethics Committee
MES Medical College, Perinthalmanna

Chairman
Institutional Research Committee

Cc The Dean
MES Medical/Dental College

10. PUBLICATIONS & PRESENTATIONS

List of Publications

- "Prevalence of Gestational Diabetes Mellitus among pregnant women attending for antenatal care- A Hospital based study". **Fathima Habeeba TE**, Revikumar KG, Jaideep Mahendra, Mumtaz P, Jithesh TK & Mohammed Muneersha TK. *International Journal of Research in Pharmaceutical Sciences.* 2020, 11(4), 6897-6901
- "Efficacy of Metformin among subjects diagnosed with Gestational Diabetes Mellitus". **Fathima Habeeba TE**, Revikumar KG, Jaideep Mahendra, Jithesh TK, Mohammed Muneersha TK, Mirshad PV. *International Journal of pharmacy & Pharmaceutical Research*, 2021, 20 (2), 145-154.

List of Oral Presentations

- Done oral presentation on "Neonatal Characteristics of Gestational Diabetic Mother Treated with Different Anti-Diabetic Agents in a Tertiary Care Teaching Hospital" at a National Seminar organized by the Department of Medical Biochemistry, School of Medical Education, Centre of Professional and Advanced Studies, Kottayam, Kerala, India on 25th January 2019.
- Presented Scientific Paper on "Comparative study of Metformin versus Insulin in the Pharmacological Management of Gestational Diabetes Mellitus – A prospective study" at National Conference organized by Meenakshi Ammal Dental College and Hospital, Chennai, Tamil Nadu, Indiaheld on 30th June 2018.

List of Poster Presentations

- Done poster presentation on "Prevalence and Risk Factors in Pregnant Woman Diagnosed with Gestational Diabetes Mellitus in A Post Graduate Level Teaching Hospital in South Malabar Region" at Believers Church Medical College, Thiruvalla, Kerala on 30th June 2017.
- Done presentation on "Pattern Analysis of drugs used in management of Gestational diabetes Mellitus in a tertiary level teaching hospital" at Nirmala College of Health Sciences, Thrissur, Keralaon 8th and 9th April 2016.